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Changes in the Rhesus Monkey's EEG Responses to Ethanol During Chronic Exposure

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ALTSHULER, H. L., B. HARLAN, N. R. BURCH, R. DOSSETT, J. KENDALL AND W. BURTON. *Changes in the rhesus monkey's EEG responses to ethanol during chronic exposure.* PHARMAC. BIOCHEM. BEHAV. **13**: Suppl. 1, 233–240, 1980.—This study was designed to document the changes in the CNS response to ethanol during chronic exposure in 5 male, 3.5–5.0 kg rhesus monkeys. Electrodes were implanted bilaterally into the amygdala, hippocampus and the calvarium over the frontal and temporal cortex. Ethanol or control solutions were administered intragastrically through indwelling cannulae. The 1.25 g/kg ethanol challenge dose was administered during EEG recordings. After one challenge dose, the animals received 60 days of chronic alcohol exposure (3.0 g/kg/day increasing to 8.0 g/kg/day). EEG was recorded every 10 days and analyzed by period analysis. Changes in the effect of the challenge dose were assessed by determining the percentage change of the EEG from pre-dose levels to selected times post-dose throughout the chronic alcohol exposure. The EEG response changed significantly during chronic alcohol treatment. Although each structure exhibited a slightly different pattern of change, the overall change was a shift from an excitatory response in the non-tolerant animal to an EEG slowing during chronic exposure. We suggest that such a change may be useful as a diagnostic marker for alcohol tolerance. In addition, the differential nature of the *in vivo* expression of alcohol tolerance in each brain area suggests that such analysis may provide a valuable tool for understanding the mechanism and expression of alcohol tolerance in the CNS.

Alcohol Alcohol tolerance Frontal cortex Temporal cortex Amygdala Hippocampus Period analysis Subhuman primates

THE chronic administration of many drugs is often associated with the development of physiological and metabolic tolerance (TOL). In many cases TOL is demonstrable [15, 21, 22] by diminished responses to a drug during chronic treatment with that drug. Although there are a number of reports that describe the neurophysiological effects of the acute administration of alcohol in animals [12, 15, 16–20, 26, 27, 35] relatively few [18, 29, 37, 38] have included discussion of the changes in such measures in animal models during chronic administration. Most studies have dealt with discrete electrophysiological measures such as evoked potentials [6, 7, 9, 11, 13, 28, 33], single or multiple unit responses [14, 20, 23, 24, 25, 30, 34, 36]. There is a definite need for experimental documentation of the changes in the spontaneous or drug stimulated electroencephalogram (EEG) during the development of alcohol (ALC) TOL.

The design of experiments relating to drug TOL can be a significant factor determining the quality and quantity of the descriptive detail that is obtained. Such investigations must document changes in the resting CNS state as well as the changes in the response to the drug, since changes in the resting state of the CNS have significant effects on a drug's acute actions. This study was designed to quantify CNS responses to challenge doses (CHD) of ALC during chronic ALC exposure (CAE). Both the resting EEG (pre-CHD) and the ALC stimulated EEG were assessed periodically during CAE to permit the delineation of the changes in the resting CNS as well as its responsiveness to ALC CHD during the development of TOL.

One premise underlying the design of these experiments was that it was desirable to use measures that could also be used in a clinical population; thus both surface and deep

brain recordings were obtained. A second premise was that the route of ALC administration must be intragastric, as it is in man. The results of these experiments suggest that it may be possible to develop a diagnostic test for the detection of ALC TOL [39] in a clinical population. In addition, new information about the differential rate of development of ALC TOL in different structures of the subhuman primate brain has been established.

METHOD

Animal Subjects

Five male rhesus monkeys *(Macaca mulatta)* weighing 3.5–5.0 kg served as subjects for the study. Although the monkeys (MNKS) had all had previous exposure to psychoactive drugs, they had not received such drugs for at least 12 months prior to the beginning of this study. The MNKS were housed individually in standard primate cages, maintained on a 12 hour light/12 hour dark daily cycle, fed laboratory monkey chow ad lib and had continuous access to water. They received thorough biomedical examinations, complete blood counts and serum chemistry profiles prior to entry into the study. Such examinations and laboratory tests were repeated each week of the study.

Surgical Preparation

Food was withheld from the animals for 14 hours prior to the scheduled surgery. They were anesthesized with sodium pentobarbital (30.0 g/kg IV) and placed in stereotaxic equipment. Stainless steel screw electrodes were implanted bilaterally into the calvarium over the frontal (FC) and the temporal cortex (TC). Stainless steel bipolar electrodes (1.0 mm tip separation) were implanted bilaterally into the hippocampus (HIPP), amygdala (AMYG) and several other areas (not reported). Table 1 summarizes the stereotaxic coordinates of the deep electrodes. After all electrodes were in place the lead wires were connected to a female amphenol (Newark Electronics) electrical connector and the wires, part of the connector and calvarium were covered with dental acrylic cement.

After the CNS surgery was completed, atropine sodium (0.1 mg/kg) was administered, a laparotomy performed and an indwelling intragastric (IG) cannula implanted. The procedures for the fabrication and implantation of such cannulae were developed in our laboratory and described in detail [2,3]. The cannula was sutured in the stomach at the greater curvature, brought out of the peritoneal cavity through the abdominal musculature, tunnelled subcutaneously to the animal's mid-back and exteriorized through a small skin incision. The MNKS were fitted with cloth jackets (Medical Arts, Inc.) or stainless steel harnesses [10] to protect the cannulae. A thirty day recovery period followed and included frequent diagnostic tests, treatment of postoperative infections, and tests of the function of the cannula and electrodes. Animals entered the study formally when all biomedical and experimental parameters were normal.

EEG Recording Experiments

The MNKS were seated in primate restraint chairs (Paslab, Inc.) in a darkened, sound attenuated room for each EEG recording experiment. A shielded cable was used to connect the electrode plug on the animal to a Beckman Accutrace (TM) 16 channel Electroencephalograph. The amplified signal was transmitted from the electroencephalograph to period encoders [1,8] for on-line data reduction. The period encoded data was written on digital tape and processed off-line on a Cybor 70 (Control Data) computer for final data reduction, analysis and summary. Each experiment consisted of 30 min of pre-dose recording and 90 min of recording after doses of ALC, saline (SAL) or glucose (GLU).

TABLE 1
STEREOTAXIC COORDINATES (mm)

Structure	R-L	AP	Depth
Frontal Cortex	13.0	A:20.0	—
Temporal Cortex	25.0	A:12.0	—
Hippocampus	10.0	A:07.5	−4.0
Amygdala	08.0	A:01.2	−1.0

Drug Solutions

All drugs were administered via the IG cannula. An extension cannula was used to allow the injections to be given from outside the recording chamber or home cage without disturbing the MNKS. ALC as either the chronic dose (CD) or the CHD was administered as a 15% w/v solution. The control solutions were both 0.9% SAL in volumes equal to the largest volume ALC dose, or 5% GLU in doses that were calorically equivalent to the calories contained in the largest ALC dose.

Analysis of Electrophysiological Data

The electrophysiological data were reduced and analyzed with period analysis (PA [8, 31, 32]). PA analyzes the EEG in the time domain by describing the time relationships of the certain critical points of the EEG wave. Such critical points per unit time are: the isoelectric line crosses (major period counts; MPC), the number of minima and maxima points (intermediate period counts; IPC) and the number of points of inflection in the primary signal (minor period counts; MIC). This technique does not quantify amplitude, although the relationships between frequency and amplitude are implicit. Table 2 summarizes the mathematical basis of PA and its relationship to power-spectral density analysis [31]. Figure 1 presents a graphic illustration of the critical points counted by PA.

ALC Exposure

The chronic dosage schedule was designed to increase the daily ALC exposure as rapidly as possible in order to optimize the development of TOL and physical dependence. Chronic doses were administered IG beginning at 3.0 g/kg/day, gradually increased to 8.0 g/kg/day by Day 20 and maintained at that level from Days 20–60.

Prior to this study, acute dose-response relationships were established for IG doses of 0.25 g/kg–2.5 g/kg. 1.25 g/kg IG was selected as the CHD and administered on Day 1 and every 10 days thereafter during EEG recording sessions. Table 3 summarizes the overall protocol and dosage regimen and illustrates the distinction between the CHD and CD.

TABLE 2

RELATIONSHIPS OF PERIOD ANALYSIS AND POWER SPECTRAL DENSITY ANALYSIS

N = number of baseline crosses per second of the EEG
N_1 = number of baseline crosses per second of first derivative of the EEG
N_2 = number of baseline crosses per second of second derivative of the EEG
$P(f)$ = power spectral density of the EEG

$$\text{major} = (N/2)^2 = \frac{\int_R f^2 P(f)df}{\int_R P(f)df} = \text{second moment of normalized power spectral density}$$

$$\text{intermediate} = (N_1/2)^2 = \frac{\int_R f^4 P(f)df}{\int_R f^2 P(f)df} = \frac{\text{fourth moment of power spectral density}}{\text{second moment of power spectral density}}$$

$$\text{minor} = (N_2/2)^2 = \frac{\int_R f^6 P(f)df}{\int_R f^4 P(f)df} = \frac{\text{sixth moment of power spectral density}}{\text{fourth moment of power spectral density}}$$

Data Analysis and Statistical Testing of Significance

PA provides data in the form of counts/unit time (usually seconds). In this study the mean of 60, 1.0-sec period counts formed the essential data for each minute of the experiments. In addition, the data from all MNKS were averaged to produce group mean data. The primary assessment of the actions of ALC was based on comparing the pre-dose EEG to the post-dose EEG. The difference was expressed as the percentage difference between the mean period counts from selected minutes of pre-dose EEG and an equivalent number of minutes of EEG at specified times post-dose.

The primary measure of the effect of CAE and actions of ALC was the change in the EEG response to the ALC CHD at selected times during chronic exposure and the unique changes in each brain structure. Since these data were distributed normally, a parametric test of significance (Students "*t*") was used to evaluate those differences.

RESULTS

These experiments revealed significant changes in the electrophysiological response of each brain structure to CHD of ALC during 60 days of CAE. Important differences between the structures were found in the time of onset and the magnitude of the effect observed.

Animal Health and General Behavior

Repeated physical examinations, clinical biochemical, and hematological indexes documented that the animals completed 60 days of chronic ALC exposure in satisfactory health. There were some expected changes in the serum chemistries that suggest the onset of ALC related hepatotoxicity after 42 days of CAE, although it was not necessary to remove any animal from the study. Although the animals appeared inebriated most of the time, they generally maintained sufficient functional levels to consume

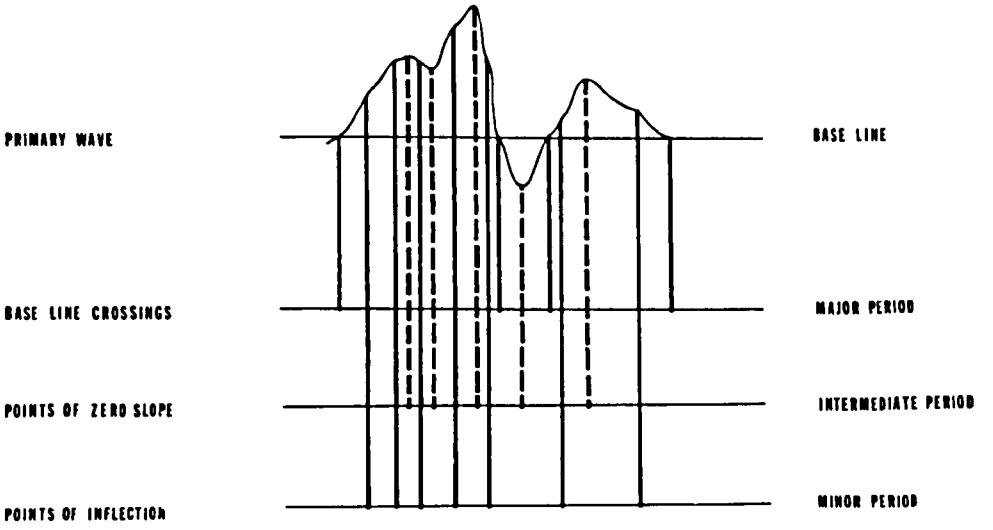

FIG. 1. Critical points of the EEG wave detected by period analysis.

TABLE 3
ALCOHOL DOSAGE SCHEDULE

Day of Study	Challenge Dose	Chronic Dose	Total Daily Dose
1	1.25 g/kg	1.0 g/kg × 2	3.0 g/kg
2–9		1.0 g/kg × 3	3.0 g/kg
10	1.25 g/kg	1.5 g/kg × 2	4.25 g/kg
11–15		1.5 g/kg × 3	4.5 g/kg
15–19		2.0 g/kg × 3	6.0 g/kg
20	1.25 g/kg	2.0 g/kg × 2, 0.75 g/kg × 1	6.0 g/kg
21–24		2.0 g/kg × 3	6.0 g/kg
25–29		2.0 g/kg × 4	8.0 g/kg
30	1.25 g/kg	2.0 g/kg × 3, 0.75 g/kg × 1	8.0 g/kg
31–39		2.0 g/kg × 4	8.0 g/kg
40	1.25 g/kg	2.0 g/kg × 3, 0.75 g/kg × 1	8.0 g/kg
41–45		2.0 g/kg × 4	8.0 g/kg
46	1.25 g/kg	2.0 g/kg × 3, 0.75 g/kg × 1	8.0 g/kg
47–49		2.0 g/kg × 4	8.0 g/kg
50	1.25 g/kg	2.0 g/kg × 3, 0.75 g/kg × 1	8.0 g/kg
51–59		2.0 g/kg × 4	8.0 g/kg
60	1.25 g/kg	2.0 g/kg × 3, 0.75 g/kg × 1	8.0 g/kg

most of their food ration each day. No clinical evidence of malnutrition was observed and all MNKS gained some weight during the study.

Electrophysiological Results

Significant changes in the responses of the FC, TC, AMYG and HIPP to ALC CHD were found during CAE. The changes differed in each structure especially regarding the duration of CAE preceding the maximum responses to the ALC CHD. In this study, as in our previous work [4], SAL or GLU produced no EEG effect after acute or chronic doses.

Frontal Cortex

The prototypic FC response to ALC CHD in non-tolerant MNKS was the gradual increase in MPC during minutes 1–15 post-dose to 12.1 ± 0.6% above pre-dose levels ($p<0.05$). The MPC remained elevated for the duration of the experiment. By Day 10 of CAE the FC response to the CHD converted to a 21.0 ± 1.2% MPC decrease below pre-dose levels during minutes 1–15. The MPC remained at that level for the duration of the experiment. Figure 2 summarizes the minute-by-minute MPC changes during an entire recording and compares the responses on Day 1 and Day 60. The minute-by-minute differences between the Day 1 and Day 60 MPC were significant ($p<0.01$).

Figure 3 summarizes the FC response to ALC CHD 75–79 minutes post-dose on each recording day of CAE. It should be noted that the 75–79 minute MPC on Day 1 was 11.3% higher than the pre-dose MPC. By Day 10 of CAE the 75–79 minute post-dose MPC was 17.1% below the pre-dose MPC. Although the magnitude of the post-dose MPC decrease fluctuated somewhat during the study, it is important to note that during the entire CAE the FC response to ALC CHD consisted of a decreased MPC. In contrast, on Day 1, the response was an increased MPC.

Temporal Cortex

There were marked differences between the TC and FC in the rate of development of electrophysiological signs of TOL. The prototypic response to ALC CHD of the non-tolerant TC was biphasic, consisting of an initial small MPC increase (early component) followed by a return to pre-dose levels (late component). The early component of the TC response converted to an MPC decrease during CAE. In contrast to the FC, the maximum decrease ($p<0.01$) in the MPC of the TC occurred on Day 40 instead of Day 10. The late component of the TC response also changed during CAE. The magnitude of the late component MPC decrease became greater during CAE; and the maximum effect occurred on Day 10 ($p<0.05$) in contrast to the early component that exhibited the maximum change on Day 40. Figure 4 summarizes the changes in the early component of the TC response to ALC CHD and Fig. 5 summarizes the changes in the late component.

Amygdala

The non-TOL AMYG also exhibited a biphasic response to ALC CHD. An important part of the early response component of the non-TOL AMYG was an 18.6 ± 3.1% increase in the IPC 3–7 minutes post-dose ($p<0.05$). The magnitude of the IPC increase became reduced during CAE and by Day 60 was no longer observable (Fig. 6). The late component of the AMYG response consisted of 26.4 ± 3.8% increase in the MPC on Day 1 ($p<0.01$). A decrease in the MPC was observed after 10 days of chronic ALC. The maximum MPC decrease in the late component of the AMYG response occurred on Day 20 ($p<0.05$) and then gradually disappeared (Fig. 7).

Hippocampus

The non-TOL HIPP also exhibited a biphasic response to

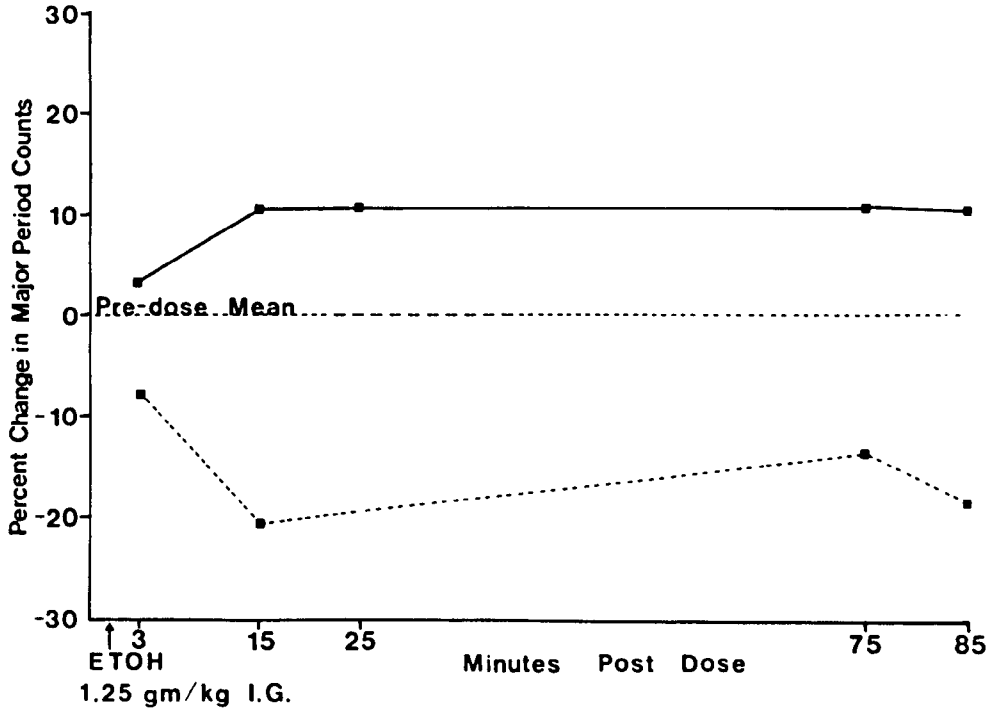

FIG. 2. Comparison of the post-dose MPC recorded from the FC on Day 1 and Day 60 of chronic ALC exposure. This figure summarizes the MPC of the FC response to ALC CHD in recordings obtained on Day 1 and Day 60. The ordinate represents the percent change of the post-dose MPC from the pre-dose MPC. The pre-dose MPC is represented by zero on the ordinate. The change in the post-dose MPC on Day 1 is represented by the solid line and the Day 60 change by the broken line. The time post-dose is represented on the abscissa. The arrow on the abscissa depicts the IG injection of the ALC CHD.

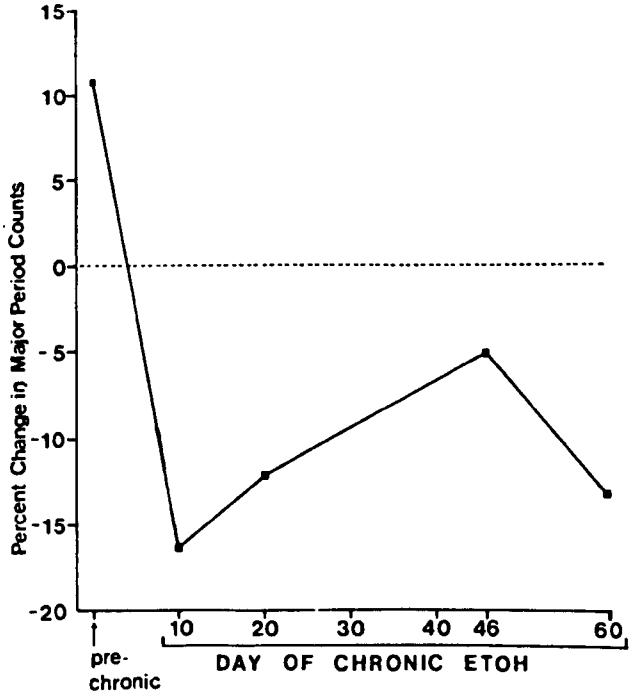

FIG. 3. Changes in the MPC of the late component of the FC response. This figure summarizes the changes in the MPC of the late component of the FC response to ALC CHD during chronic ALC exposure. The ordinate represents the percent change of late component MPC compared with pre-dose MPC. The pre-dose MPC is represented by zero on the ordinate and the horizontal broken line. The abscissa represents the day of the study. The arrow represents the response on Day 1 (pre-chronic).

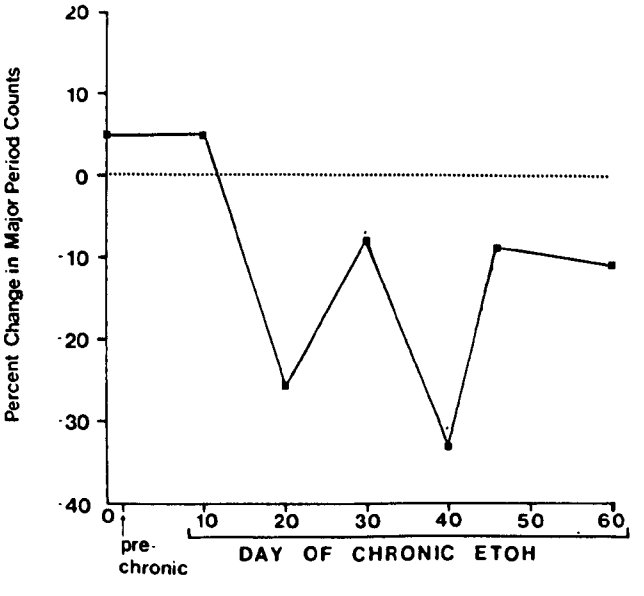

FIG. 4. Changes in the early component of the TC response during chronic ALC. This figure represents the percent change in MPC from pre-dose to 5–9 min post-dose on each day of chronic ALC exposure. The ordinate represents the percent change from pre-dose. The pre-dose MPC is represented as zero on the ordinate and the horizontal line at that position. The abscissa represents the day of the study. The arrow on the abscissa indicates Day 1.

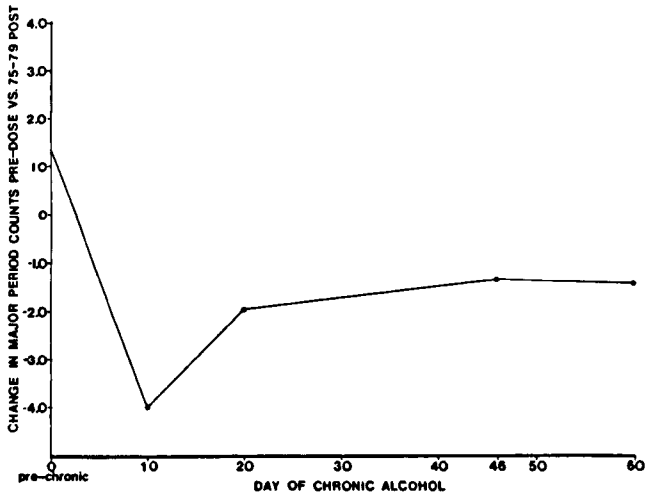

FIG. 5. Change in the MPC of the late component of the TC response during chronic ALC exposure. This figure presents the changes in the pre-dose vs post-dose difference in the MPC of the TC response to ALC CHD. The effect is shown as mean difference in MPC between pre-dose and 75–79 minutes post-dose and is represented on the ordinate. The abscissa represents the day of the study.

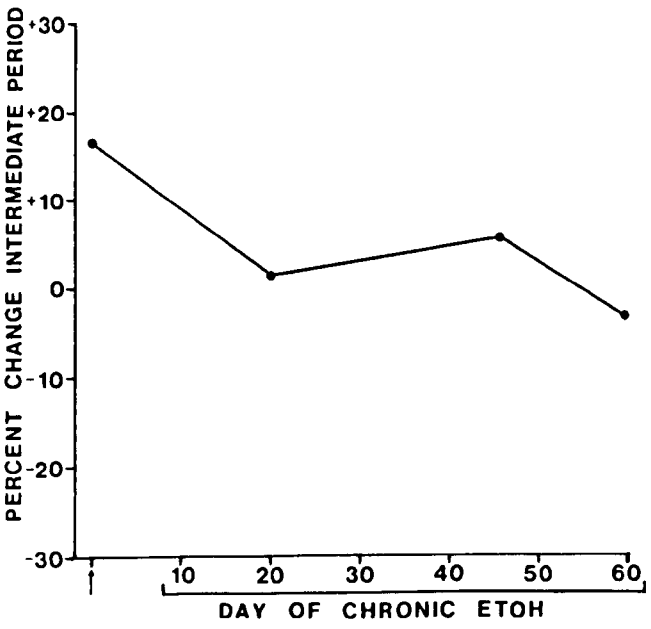

FIG. 6. Intermediate period changes in the early component of the AMYG response to ALC CHD during chronic ALC exposure. The ordinate represents the percent change from the pre-dose IPC after the ALC CHD on test days during chronic ALC exposure. The pre-dose IPC is represented by the zero on the ordinate. The abscissa represents the day of the study. The arrow on the ordinate indicates Day 1 (pre-chronic).

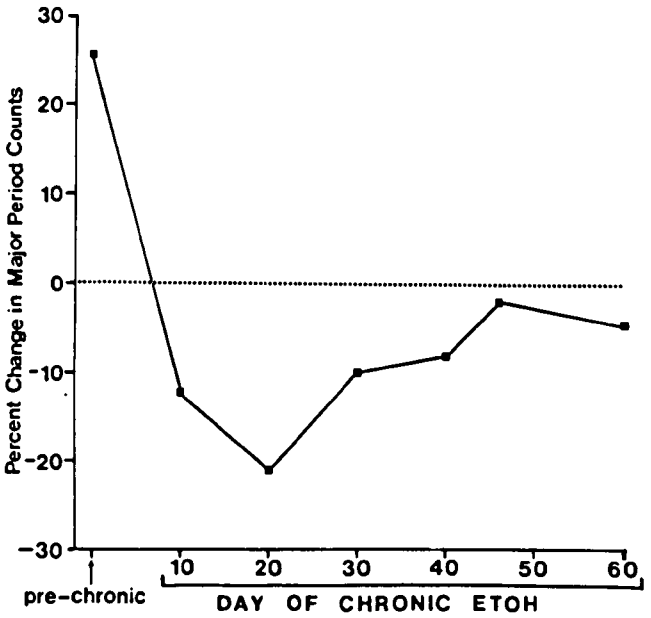

FIG. 7. Percent change of MPC of the late component of the AMYG response to ALC CHD on test days during chronic ALC exposure. The ordinate represents the percent change in MPC from pre-dose to 75–79 minutes post-dose on each test day. The mean pre-dose MPC is represented by zero on the ordinate. The abscissa represents the day of the chronic study. Day 1 (pre-chronic) day is indicated by the arrow.

ALC CHD. On Day 1 the 3–7 minutes post-dose MPC was 13.3. During CAE the early component MPC gradually decreased to 9.7 by Day 40 (Fig. 8). The pre-dose MPC on all days ranged from 10.8–11.4. Therefore, the primary change in the HIPP response during CAE was loss of the initial MPC increase following ALC CHD that comprised the early response component. There were no significant changes in the late component of the HIPP response to ALC CHD.

DISCUSSION

The results of these experiments demonstrated that there were important changes in the electrophysiological responses to ALC in two cortical areas (FC, TC) and two deep brain structures (AMYG, HIPP) during CAE. In addition, each structure differed with regard to rate of development of such changes. The differences between the structures were manifested as quantitative and qualitative differences in the effects of CAE on the early and late components of the characteristic response of each structure. The general effect of CAE and related TOL in all the structures was the conversion of the ALC CHD induced activation and acceleration (increased MPC) in the non-TOL animal to a consistent slowing (decreased MPC) of at least one component of the response in the TOL animal. We suggest that such changes may be useful in the future as a diagnostic marker [39] for the presence of ALC TOL.

There were distinct differences in the rate of development of the CAE related changes in each structure studied. For example, the maximum MPC decrease of both the early and

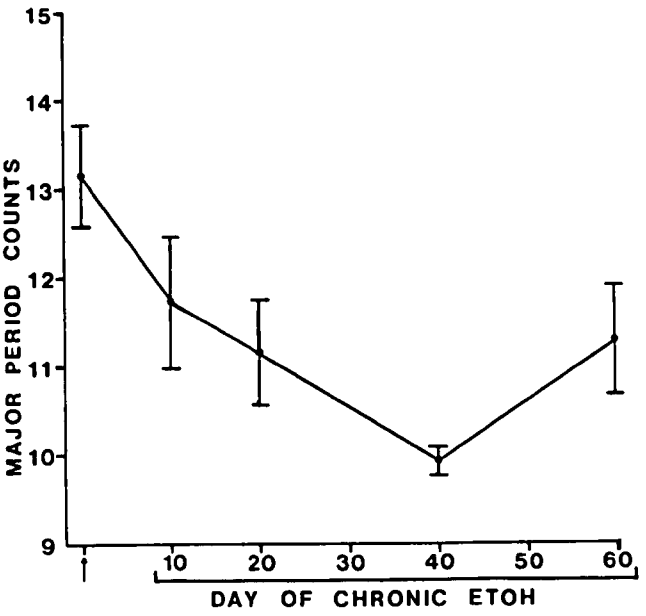

FIG. 8. Change in MPC of the early component of the HIPP response during chronic ALC. The ordinate represents the 3–7 minutes post-dose MPC on all test days. The pre-dose MPC ranged from 10.8–11.4 on all test days. The abscissa represents the day of the study. The arrow on the abscissa represents the Day 1 (pre-chronic) test.

late components of the FC response occurred on Day 10. However, in the TC and HIPP the maximum change in the late component did not occur until Day 40. In addition, CAE related changes also occurred in the rate of change of each of the components of the response of a single structure. For example, the maximum MPC decrease in the late component of the response in the TC and HIPP occurred on Day 40, but the maximum change in the early component of the response in those structures occurred on Day 10.

The changes in the AMYG response during CAE differed from those in other areas, particularly in the late component of the response. During early CAE the late component of the AMYG response consisted of a decreased MPC that was quite similar to the other structures. However, unlike the FC, TC and HIPP, in the AMYG the magnitude of the late component MPC decrease diminished after Day 20.

These results are different from those obtained in a previous study [5] where we observed a potentiation of the early component of the response to ALC CHD during CAE. The major difference between that study and the present one was that in the previous study all ALC doses were given IV and in the present study they were given IG. The difference in the route of administration is probably sufficient to account for the discrepancy between the results of the two studies. The gradual increase in ALC concentration at the target sites following IG dosage [4] presents a quite different stimulus to the neurons than the rapid increase following IV dosage. It has been suggested [21,22] that TOL development is maximized by the continual presence of ALC in neuronal target areas. Although IG dosage does not provide constant ALC levels, quite slow absorbtion and metabolism have been shown [4] to be associated with frequent IG dosage in MNKS.

Other laboratories have reported slightly different outcomes of similar studies as this one. Triana *et al.* [37,38] reported initial increases in CNS irritability of MNKS during CAE by the nasogastric route. The irritability disappeared after 9 weekly trials, apparently after TOL developed. The present study did not examine responses before 10 days of CAE. It is entirely possible that both the Triana *et al.* [37,38] studies and this one would have found similar CNS changes if the observations were made after equivalent CAE.

It is interesting to note that the results of the Triana *et al.* study were generally consistent with the results of our previous study in which the CAE was by the IV route, but the dosage regimen was identical to the present study. It is likely that the IV route used in our previous study did not induce ALC TOL to the same extent as the IG exposure used in the present study. Furthermore, it is possible that the CNS changes resulting from ALC TOL due to chronic IV dosage were analogous to those resulting from shorter duration, less frequent IG administration. Unfortunately, there is relatively little information available about the effect of the route of ALC exposure on the rate of development of ALC TOL. The generally held notion that constant blood levels of ALC are more effective inducers of TOL than fluctuating levels would support this hypothesis and would partially explain the differences and similarities between the three studies discussed.

One of the most promising findings of this study was the consistent change in the FC response during CAE. We suggest that a CAE related change of that type may provide a clinically useful, rapid diagnostic test for the assessment of ALC TOL. Due to the potential importance of such a marker and its observed robustness, we consider the extension of these studies to be of extreme importance. Furthermore, we suggest that the correlation of these findings with the neurochemical changes that accompany ALC TOL would add a new dimension to our understanding of ALC TOL and its *in vivo* expression.

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